WOUND INFECTIONS

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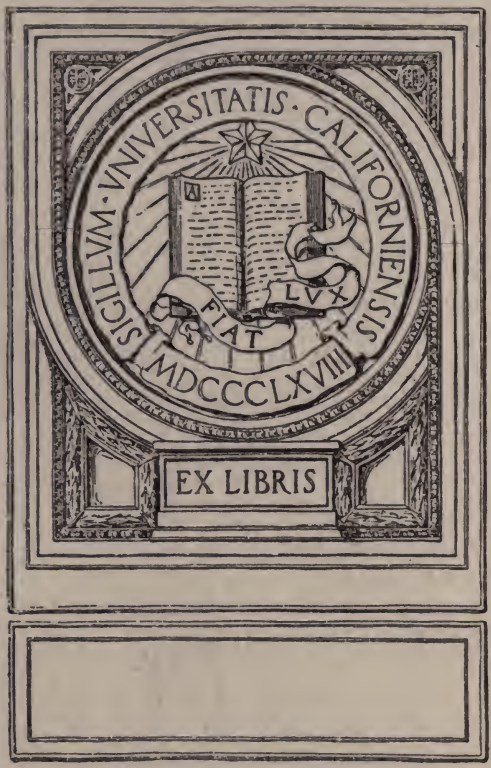
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WOUND INFECTIONS

WOUND INFECTIONS

AND SOME NEW METHODS FOR THE STUDY OF THE VARIOUS FACTORS WHICH COME INTO CONSIDERATION IN THEIR TREATMENT

BY

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Being an Address delivered before the Royal Society of Medicine, and taken from the Research Laboratory attached to No. 13 General Hospital, Boulogne-sur-Mer

University of London Press, Ltd.

AT ST. PAUL'S HOUSE, WARWICK SQUARE, LONDON, E.C.

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WOUND INFECTIONS.

CHAPTER I.

Biological Evolution of Wound Infections.

THERE are a number of quite elementary problems which must be solved before we can arrive at any really effective treatment of wound infections. A very brief consideration of the facts will bring us face to face with the questions to which we have to find an answer.

In this war practically every wound is heavily infected. The chain of cause and consequence seems to be as follows: The clothes and skin of the soldier on war service become contaminated with all manner of filth containing pathogenic organisms and spores; the projectile takes these in with it, and it implants them far in—in point of fact, far beyond the reach of any prophylactic applications of antiseptics.

A cultivation medium is now provided by the blood and lymph which are poured out into the track of the projectile; and we find in the wounds—I have in view here wounds examined immediately after arrival from the Front—a mixed infection of a streptococcus with microbes derived from the fæces (fig. 1). This fæcal infection is a special outstanding feature in this war.

Among many species of intestinal microbes which have been found in wounds, two have a quite special importance. One is the *gas-phlegmon bacillus*, or *Bacillus aerogenes capsulatus* of Welch — a large Gram-staining, anaerobic and actively gas-forming microbe. It is found both in infiltrated superficial wounds and in deep wounds, and is particularly abundant in the frothy and offensive fæcal-looking discharges which anaerobic wounds furnish. The other is the tetanus bacillus. This is more rarely encountered, and is also much less abundant in the discharges. Sometimes, however, it may show up in every field of the microscope.

The presence of the streptococcus and these two fæcal microbes makes the first period of the wound infection—the period of imprisoned discharges—a specially critical time for the patient. During this the streptococcus may invade the tissues, and set up cellulitis or, more rarely, erysipelas. Or the

FIG. 1.

Film from a recently inflicted wound showing *B. tetani*, *B. aerogenes capsulatus*, pyogenic cocci, *B. proteus*, and putrefactive bacilli.

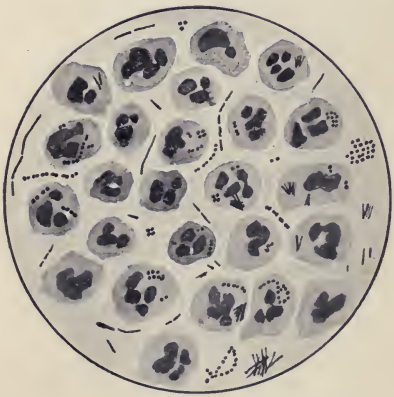


FIG. 2.

Film from a wound showing a late stage of infection. Streptococcus, staphylococcus, anaerobic diphtheroid bacillus, largely phagocytosed; *B. proteus*, all extracellular.

Face p. 2.

tetanus bacillus may find opportunity to grow out and manufacture its poison and induce tetanus. Or the bacillus of Welch may make its way into the body and set up a gas-phlegmon in the region round about the wound, and an obstructive gangrene in the distal portion of the limb. Or, again, the bacillus of Welch and the streptococcus may join forces, and may in conjunction produce the gas-phlegmon or cellulitis.

As soon as a free outlet has been provided, and aerobic conditions have been established in the wound, its bacterial flora changes. The ordinary pyogenic infection, which has up to this been in abeyance, now gains the upper hand, and instead of an "*infection of the imprisoned discharges*," or, as the case may be, *an infection of tissues*, we have now an "*infection of the granulating wound surfaces, and of the flowing discharges.*" The chief bacterial agents here at work are the streptococcus and staphylococcus, and *Bacillus proteus* (fig. 2).

This pyogenic infection may, after lapse of time, subside—the wound healing up when this occurs; or the mixed infection may narrow itself down to a streptococcic infection and become chronic, the wound in this case remaining open indefinitely in the form of a discharging sinus. Or, lastly, when

there is an obstructed outflow, the infection may go from bad to worse until the patient succumbs to continued suppuration and septicæmia.

Some Fundamental Considerations in regard to Treatment.

Those are, in very brief summary, the facts with regard to the evolution of wound infections, and I would venture, in passing on to discuss with you their treatment, to remind you that the ideal we ought to approximate to is the healing of the wounds by *first intention*—that is, without sensible interference by bacterial infection; and that so far are we from the attainment of that ideal that nearly all our wounded are suffering from bacterial infections; that very many are ill of these infections; and that not a few are, through these, in danger of their lives.

We have at our disposal for the treatment of these wound infections three distinct therapeutic measures. Let me enumerate them in the order in which they would naturally suggest themselves to you.

First in that serial order would come *treatment by antiseptics*. After this would come what I propose to call *treatment by physiological methods*

—I mean procedures such as the opening and draining of the wound — which bring the antibacterial powers of the blood to bear on the infecting microbes. And lastly would come the reinforcement of the antibacterial powers of the blood, that is, *treatment by vaccine therapy* and similar methods. I believe it is really above all question that of these three the second is beyond all comparison the most important, and I would submit that—all loud talk about it notwithstanding —antiseptic treatment is at best an ancillary method of treatment. And of course the same applies also to treatment by vaccines.

Let me also here suggest to you another quite fundamental consideration. It is this: It will be clear that we cannot apply physiological treatment aright, nor can we use any antiseptic or vaccine to best advantage in wound infections, unless we first understand the physiological processes going on in the wound. We do not yet understand these even in outline.

It will therefore be necessary to address ourselves to the task of discovering what goes on in the wound and of following up its biological evolution. And the only way of doing this will be to formulate to ourselves in clear terms the questions which want answers; then to consider how to set to

work to get our answers—for merely looking at the wound will not help; and finally to take cognisance of the results which the experimental methods I am about to describe to you have already yielded.

Our first question can be formulated thus:—

(1) *Can the microbes which are found in wound infections live and multiply in the unaltered blood fluids?*

In other words, if I take pyogenic microbes from the wound and implant these into the normal undiluted serum, will they grow freely? If we are going to carry out this experiment, and to carry it out repeatedly, and deal with a number of different bloods; and if we are going to cultivate directly from the pus, we shall evidently have to work in capillary tubes with very minute quantities of pus and very small quantities of undiluted serum. The technique which I have arrived at for fulfilling these requirements is a very simple one. I may call that technique the *wet-wall method.*

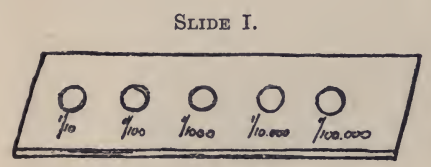
Method of making Cultivations of Pus in Serum, by the Wet-wall Method.

The first step in the procedure is to make, by the technique I described in my book on "Technique,"[1] a graduated series of dilutions of pus, using for this purpose any indifferent diluting fluid, and arranging the successive dilutions on a slide in the form of a series of drops (fig. 3, slide I). I then take in hand a clean capillary pipette fitted with a teat, make a mark upon the stem, and then draw up into it a series of unit volumes of serum, one unit volume of serum for every dilution of the pus. This done, I commence with the highest of these dilutions—that is, the one containing the smallest number of microbes—and draw it up into the stem of the pipette, stopping off exactly at the fiducial mark (fig. 4). I then expel this column, leaving, of course, as I do so, the walls wet with a quantum of microbial suspension — a quantum which would correspond roughly to that which would be left on the outside of a platinum wire of similar stoutness dipped into the suspension. I

[1] "Technique of the Teat and the Capillary Glass Tube," Constable, London.

now expel from my capillary tube my first volume of serum—this in passing over the wet wall will take up its charge of microbes—and I receive this as it issues on to a clean slide. I repeat these manipulations with the next lower dilution of pus and the next unit volume of serum, and so on, until I have implanted my series of volumes of serum with my series of bacterial dilutions. At the end I find myself with a series of drops of serum containing graduated charges of microbes, ranged in order upon a slide (fig. 3, slide II) ; and I have in my hand a pipette which is contaminated up to the point indicated by my fiducial mark. I get rid of this contaminated segment of my capillary stem by resecting this just above the fiducial mark, and I now proceed to draw up into my pipette, separating off by bubbles of air, the whole series of drops of serum, beginning with that implanted with the fewest microbes. After sealing up the distal end of the pipette, and closing the butt end by bringing it down upon a bed of plasticine, the pipette is placed in the incubator. After an interval of six to twenty-four hours it is taken out, and the series of unit volumes are now, for purposes of microscopic examination or culture, expelled from the pipette in the order in which they have been taken up—that is, in succession from the lightest

to the heaviest implanted. This is effected by cutting through the proximal end of the stem of the pipette and then the distal end, and afterwards



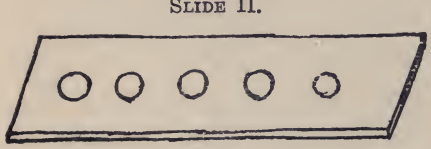


FIG. 3.

Slide I: Graduated dilutions of pus arranged on slide. Slide II: Volumes of serum implanted with the above dilutions of pus.

FIG. 4.

Fig. 4.—Capillary pipette filled with five unit volumes of serum and one unit volume of the last dilution of pus.

luting the latter air-tight into the truncated end of the pipette. The luting is done by rolling a little plasticine into a ball, pressing the capillary stem into this pellet as we hold it between finger and thumb, doubling over the plasticine round the stem; and then invaginating the capillary stem, thus cushioned, into the neck of the pipette. We can now with a teat expel our series of unit volumes of serum on to a slide, obtaining them in the serial order which avoids the contamination of the lighter implanted with the heavier implanted.

Method of making Anaerobic Cultures in Capillary Tubes.

When we desire to make anaerobic serum cultures we do not employ the capillary pipette used for the original implanting operations as a receptacle for our series of serum cultures, but employ instead a separate capillary cultivation tube for each unit volume of serum. The capillary cultivation tubes here in question are made as follows: We take a portion of capillary stem, say some 8 cm. long, draw it out at one end in the flame of a by-pass into a hair-fine tube, and then break it off, leaving a certain length of throttle attached. We now introduce the other end of the capillary stem

into the flame of our Bunsen, and let gravity bend it round into a siphoning curve.

Taking one of these capillary cultivation tubes we bring down the siphon end upon our drop of serum (fig. 5, A), and let this run in, afterwards tilting the tube so as to take in, as a rear-guard, a good-sized

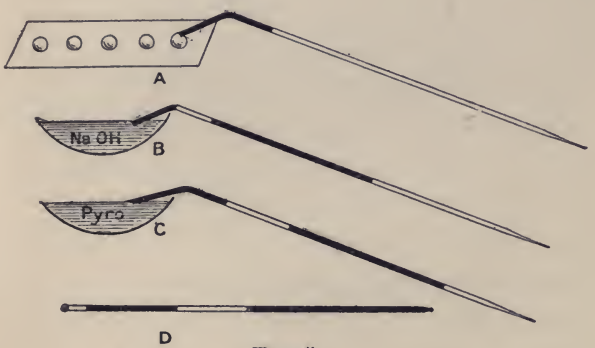


FIG. 5.

Method for making anaerobic cultures in capillary tubes.

dividing bubble of air. This done, we fill into our tube, by siphonage, from watch-glasses placed conveniently to hand, first a small quantity of pyrogallic acid, and then, without dividing off, a small quantity of caustic soda (fig. 5, B and C). We now further incline the tube, and let the contained fluids

gravitate down towards the distal end until the serum begins to enter the throttle. At that point we arrest it by sealing the tip, and we finally also seal up the butt end, leave the mixed pyrogallic acid and caustic soda to do their work and absorb all the oxygen from the dividing air bubble (fig. 5, D).

Serum cultures made by this method furnish a very striking and uniform result. We obtain in the cultures implanted with the higher dilutions of the pus a pure culture of the streptococcus, and in the cultures more heavily implanted with the pus the streptococcus mixed with a certain number of other microbes: in particular, a few staphylococci and an anaerobic wisp-like diphtheroid bacillus which often is abundant in pus, being found both intracellularly and extracellularly. All the other pyogenic microbes appear to be inhibited in undiluted normal serum, and when they put in an appearance it is only after fairly heavy sowings with pus, and comparatively late.

Out of these facts would come what we shall presently see to be a practically important classification of pyogenic microbes—a classification into, on the one hand, *serophytes;* and, on the other, *sero-saprophytes.* The serophytes would be those which, presumably because they find their foodstuffs ready made in the blood fluids, are at home there,

and can, in the absence of phagocytes, grow and multiply there without restraint, or practically without restraint.[1] The sero-saprophytes would be those which cannot grow and multiply in the blood fluids until a change—which we may, pending nearer investigation, call simply a *degenerative* change—has passed over those fluids.

What holds true of the blood fluids themselves might perhaps justifiably be assumed to hold true also of the lymph which pours into the wound. None the less, it will be well specially to investigate this point.

(2) *Does the lymph which pours into the wound provide a favourable nutrient medium for the microbes which have been growing in that wound?*

To pose this question is already to go a long way towards getting an answer to it; for we can, by the aid of a very simple device, obtain the lymph from the walls of the wound. I employ for this purpose what I may perhaps call a *lymph leech*. This consists, as you see, of a small glass tube. It is sealed up at one end, drawn out at the other in

[1] I introduce this qualifying clause because I have on several occasions found the serum of the infected patient to give cultures of streptococcus with a planting of his pus much smaller than that which was required to give a culture in the serum of a normal man.

the form of a nozzle, and is furnished with a lateral mouth with a raised rim—the whole being very easily made out of a piece of glass tubing, or small test-tube. To the nozzle we fit a piece of fairly thick walled rubber tubing, and this is blocked at the end with a piece of glass rod. When we want to obtain the exudate from a wound we bring down the lateral opening of the lymph leech upon a granulating surface, and then, transfixing the rubber tube with the needle of a hypodermic syringe, we draw out the air and make a negative pressure (fig. 6). It will be appreciated that the lymph leech is in principle merely a small cupping glass, and that it will, by means of the vacuum we establish in it, hold on tight for whatever period may intervene between dressing and dressing, and furnish an exudate free from all contamination with residual pus left behind in the wound. We can now proceed to compare the fluid in the cavity of the leech with the fluid in the wound outside; or, in connexion with work on antiseptics, to compare the contents of leeches applied respectively to treated and untreated surfaces in the same wound.

And lymph leeches also can be put to other uses. We can introduce for this purpose with a syringe any fluid we may select into the lymph leech, and investigate the effect that fluid exercises upon

transudation and emigration. Again, where the nature of a deep-lying infection of a mucous or other surface remains uncertain, the application of a lymph leech might clear up the difficulty. We can also, in the case where we are testing the effect of a vaccine upon a wound, take to our aid the

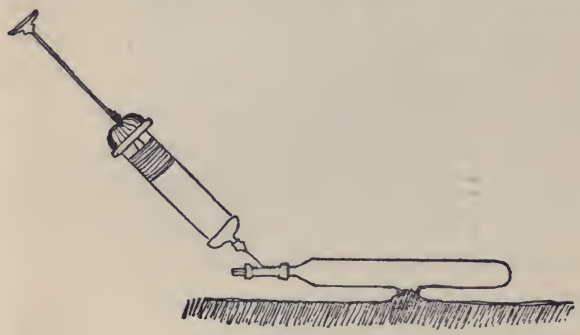


FIG. 6.
Lymph leech.

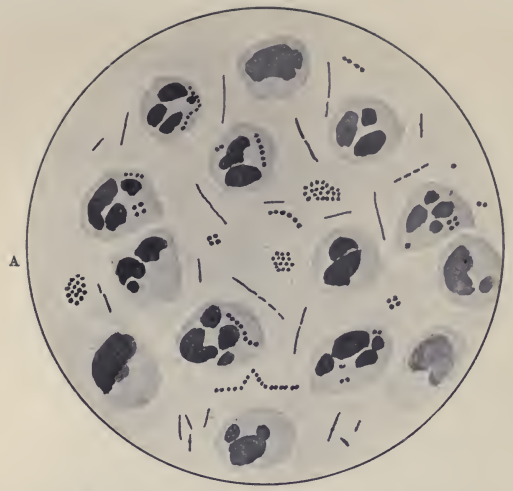
lymph leech. For the effect of a vaccine would probably show itself in the exudate in the cavity of the leech long before it would manifest itself in the outside wound. And, lastly, the application of a lymph leech to the site of inoculation might, perhaps, help to resolve the problem as to whether or no protective substances are then developed.

But it will be realised that for us—at the moment —what is of chief interest is the comparison of the

fluid in the cavity of the leech with the fluid in the wound outside.

When, after washing out a heavily infected wound with an antiseptic or simple saline solution, we apply a lymph leech to the walls, and then at the next dressing compare the contents of the lymph leech with the fluid outside, we think at first that there must be some mistake. Outside we have an opaque exudate presenting all the ordinary physical characters of pus containing leucocytes in all stages of degeneration, and swarming with all manner of pyogenic organisms (fig. 7, A). Inside we have a transparent and slightly blood-stained exudate containing streptococci in practically pure culture, and in addition a few leucocytes, all of which are actively phagocytic (fig. 7, B). Except in this latter respect, we have, in fact, identically the same result as when we made our thin implantations of pus into normal serum.

The problem now stares us in the face—What is it that makes all this difference between the contents of the lymph leech and the contents of the wound? How has the lymph, which gives in the cavity of the lymph leech only a culture of streptococcus, been converted in the wound outside into a fluid which is ideally favourable to the growth of a great number of different species of micro-organisms?



Film of pus from a granulating surface around the lymph leech, showing staphylococci, streptococci, and *B. proteus*, with many pus cells. (This hardly shows the full extent of the degeneration of the pus cells, but it was found difficult to portray this degeneration accurately.)

Film made from the contents of a lymph leech applied to the same wound, showing pure culture of streptococci with few pus cells and some red blood corpuscles.

FIG. 7.

Illustrating the bacteriological findings outside and inside the lymph leech.

Face p. 16.

(3) *What is the cause of that "corruption of the lymph" which converts it into a favourable nutrient medium for sero-saprophytic microbes?*

The proper way to go to work upon a problem of this kind is to keep it unremittingly before the mind; for then some hypothesis will in the end suggest itself. That found, there will invariably come to notice a certain number of accepted data which the hypothesis will fail to explain. These must then be carefully re-examined to see whether they will stand fast and discredit the hypothesis, or whether they also will come in and support it. And, finally, before launching our theory, we ought to think out all that would follow from it, and then make inquisition to see our theoretical anticipations are borne out.

At any other time one would wish, before promulgating a far-reaching hypothesis, to have controlled it at every point. But we have on our hands in Europe, I suppose, already two or more millions of wound infections, and every other consideration must give way to that of accelerating the researches which we must look to in order to guide us in treating these infections.

I will therefore, before completing its verification, venture to put before you what is, I believe, the solution of the problem of the corruption of the lymph in the wound.

Let me take my departure from those facts which we were considering a moment ago, relating to the culture of pyogenic microbes in the blood fluids. You will remember that I suggested in connexion with serophytic microbes that these must find all the food materials they require ready formed in the blood fluids; and in connexion with sero-saprophytic microbes, that for these no nutrient substances would be available until the albuminous substances of the blood had undergone some sort of preparatory transformation.

I conceive that that transformation could come only by a digestive process. Now, supposing this to be so, there would come into account a counteracting influence in the serum. For we have there an anti-fermentative, or, as we usually style it, an antitryptic element, which would directly counteract any digestive element which might be struggling to come into operation. And it is clear that microbes which were dependent for their sustenance upon the products of digestive action could establish themselves in the blood fluids only on condition that this antitryptic influence was overborne.

This hypothesis furnishes, as it seems to me, an explanation of certain striking facts relating to the cultivation of microbes on blood fluids, and to bacterial infections. It, as it seems to me, explains

the finding that heavy sowings of microbes into serum are effective in giving cultures, while light sowings are not only ineffective, but lethal to the implanted microbes. For it would be only natural that the resistance offered by the antitryptic power of the blood should be overborne by the mass effect of a number of microbes operating upon a restricted or—and this would come into consideration in localised infections—a mechanically isolated quantum of blood. And, again, it would be only natural that the mass effect of a large volume of antitryptic serum would effectively quench the digestive activities of a very few microbes; and also, I think, in accordance with what we know, that microbes deprived of access to foodstuffs should perish of inanition.

Our hypothesis would also make intelligible, in connexion with infections by sero-saprophytic microbes, that frequent and heavy sowings into the blood should be required before a septicæmia can supervene upon a local infection. And again our hypothesis makes it comprehensible that there should be serious difficulty in obtaining hæmocultures, even when the microbes have gained a footing in the blood-stream.

And, lastly, our theory brings home to us that, in considering the defence of the body against

bacterial infection, we have to take into account not only *active defence* in the form of phagocytes and bacteriotropic substances which make a direct attack upon micro-organisms; but also *passive defence*—that is, protection against infection obtained by preventing microbes converting to their uses the nutrient substances of the blood fluids.

These, however, are general considerations with applications far beyond the sphere of wound infections, and we must return to the particular problem of the corruption of the lymph in the wound.

When, after treating a wound with antiseptics and leaving it clean, we find it a very few hours afterwards teeming with microbes, we are in presence of something which, in my view, urgently stands in need of explanation; for our findings both in the lymph leech and in serum cultures made with the wet-wall method from pus would seem to teach us that the sowing of microbes left behind cannot be nearly heavy enough to produce the voluminous culture found in the wound, nor yet to account for the rapidity with which the sero-saprophytes have started to grow. And, moreover, upon consideration it will appear that another powerful factor must constantly come into operation in the wound. The factor in question is the tryptic ferment which is elaborated in the phagocytes and

which is, when these break up, discharged into the surrounding medium. This tryptic ferment will come into operation under two different conditions. It will come in whenever a residue of pus—for this would contain free trypsin—is left behind in, or afterwards makes its way into, the wound. Trypsin will again come into account whenever, after the washing of the wound, leucocytes once more begin to emigrate, and phagocytose, and break down.

I see in the reduction of the antitryptic power of the lymph thus effected the prime cause of its corruption. Before attempting to obtain confirmation of this from crucial experiments, there was a set of findings to be cleared up. I had found in connexion with pus implantations made into serum that when this was heated to 60° C. for ten minutes one no longer obtained the same differential growth of streptococcus as with unheated serum; but obtained instead mixed cultures of streptococcus with sero-saprophytes, in particular staphylococcus and the wisp-like diphtheroid bacillus already made mention of. It seemed at first sight as if this could not possibly be related with a reduction in the antitryptic power of the serum; for it has, in view of the high quality of Opie's work on this question, been generally accepted from him that the antitryptic power of the serum is unaffected by

exposure to heat until a temperature approaching the coagulation point of serum is reached. In reality, however, when this is re-investigated quantitatively,[1] it emerges that the antitryptic power of the serum is reduced by one-third to one-half when we subject the serum to a temperature of 60° C. for ten minutes.

That difficulty having been removed out of the way of our hypothesis, we may proceed to take cognisance of the results of the crucial test experiments—experiments in which graduated additions of trypsin are made to serum as a preliminary to the implantation of sero-saprophytic microbes. The outcome of these experiments can be summed up in a sentence. When we add trypsin in quantities sufficient to reduce appreciably the antitryptic power, but insufficient to give us any free trypsin, the serum is converted into an eminently favourable nutrient medium for sero-saprophytic microbes.

Our hypothesis is thus very strikingly confirmed. It will be necessary hereafter to follow it into all its

[1] The quantitative method here employed was in essentials that described in my "Technique of the Teat and the Capillary Glass Tube." It was varied only in the respect that the series of trypsin, serum, and calcified milk mixtures, which are employed in that method, were taken up, not into a many-stemmed pipette, but into a long, unmounted, wide-bored capillary stem, which had, for the purpose of convenient filling in, been bent round at one end in the flame of a Bunsen into a siphoning curve.

consequences. For the present it will, however, suffice if we ponder on the fact that the antitryptic power of the blood would appear to be increased in every case of severe wound infection. We have, perhaps, here a defensive reaction of the organism directed against a possible invasion of the blood by sero-saprophytes. And we may perhaps look in this direction for an explanation of the non-specific benefit which has been observed to follow upon the inoculation of bacterial vaccines. It is clearly not impossible that the inoculation of a bacterial vaccine might contribute both to active and passive defence—to the active defence of the body against a particular microbe by calling forth a production of specific bacteriotropic substances, and to the general passive defence of the organism by calling forth a production of antitrypsin. And these two forms of immunising response would not necessarily be linked together. The production of specific bacteriotropic substances would no doubt depend upon the quantum of bacterial antigen incorporated; while the production of antitrypsin might perhaps depend upon the breaking down of phagocytes and the liberation of their trypsin.

CHAPTER II.

Experimental Investigation of the Emigration of White Blood Corpuscles into the Wound.

I pass now to consider yet another subject-matter — the emigration of leucocytes into the wound. I need not labour the point that this is a factor which may determine the issue of an infection; nor need I point out that it behoves us to acquire a control over the movement of leucocytes, and then to turn this to account, as the case may be, by activating or restraining emigration.

Broad foundations for our work have, as you know, already been laid by the brilliant researches of Metchnikoff. But it was with Metchnikoff always a question of experiments *in vivo*—that is, of experiments carried out under conditions which cannot be sufficiently simplified to give quite unambiguous answers. And we require for the elucidation of our problems and for all detail work connected therewith, absolutely simple crucial experiments, such as can only be made *in vitro*.

The line of thought which I have followed in elaborating a laboratory method for the study of the phenomena of emigration is the following : The leucocytes in extravascular blood are known to retain their emigrating power. A difficulty, however, when we are working with extravascular blood, will beset our observations, inasmuch as we have not at disposal such a containing membrane as the capillary wall. We are, in fact, in dealing with extravascular blood, confronted with a situation similar to that which would be encountered in observations *in vivo* if the capillary walls were to give way and we had to make observations on emigration in a portion of tissue which was flooded out by red corpuscles.

I had hoped at first to be able to circumvent this difficulty by taking advantage of the fact that when clotting occurs the red blood corpuscles become enclosed in a meshwork of fibrin, after the manner of fish in a net. But all my efforts to make the fibrin meshwork take over the office of a containing membrane were defeated. No matter how tenderly the clot was treated the meshes of the net broke, and hæmorrhage from the clot interfered with the observations.

A second difficulty also presented itself. When in the living body white corpuscles emigrate into

connective tissue it is possible to register their travel because they move forward through a retaining meshwork. It would not be possible to do so if they merely passed out into fluid, to be afterwards carried hither and thither by every chance convection current. Exactly the same applies to the extravascular blood. The emigrating leucocyte must be provided with some sort of scantling to move forward upon, and come to rest in.

After a time I alighted on a method which satisfies the two afore-mentioned experimental requirements, and which, as I think, provides all that is required for a quantitative estimation of emigration. Let me first tell you the general lines upon which the method proceeds, and then set out the details of the technique.

Principle of the Method employed for making Observations on Emigration.

The principle of the method is as follows: We fill in a capillary tube with blood from a prick in the finger, immediately place the capillary tube in the centrifuge, and centrifugalise until we have carried down all the corpuscles. We have now in the upper half of the tube a plasma which has been completely freed from all formed elements; and in the lower half of the tube, at the bottom, the red

blood corpuscles intermixed with a certain number of polynuclear white blood corpuscles; and above this a layer made up predominantly of white blood corpuscles—these last in the front ranks consisting almost exclusively of small and large mononuclears. The blood now clots. And this gives in the upper half of the tube a clot consisting of fibrin without any formed elements—let us call this the *white clot*—and in the lower half of the tube a clot—let us call this the *red clot*—which holds all the corpuscles in its meshes. When a chemotactic stimulus now comes into application from above, the white blood corpuscles will come out from the red clot and will travel upwards through the meshes of the white clot—afterwards maintaining their positions so as to allow of our making measurements and enumerations. We will now pass to the details of the technique.

Details relating to Apparatus and Procedure.

With regard to apparatus, all that is required is a supply of flat capillary tubes. By using flattened capillary tubes we obtain a thin clot, which can more easily be examined under the microscope.

We make these tubes—and they may conveniently be called emigration or chemotactic tubes—either out of a small test-tube, or out of a length of fairly

wide-bore glass tubing. We heat this in the blow-pipe flame until it becomes very plastic; then making a sharp outward turn with the right wrist, bend the tube round through a right angle, giving it the proper flattened conformation: and then draw out into a long flat capillary stem (fig. 8, A). We cut this through at the point where it begins to lose its flattened conformation: and so leave attached to

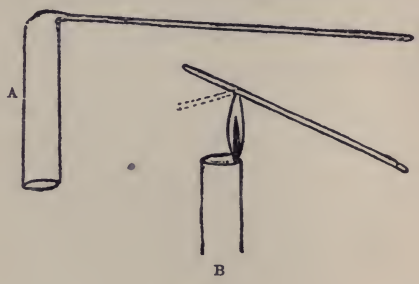


FIG. 8.

Method of making emigration tubes. A, method of giving the flattened conformation to the capillary stem; B, method of bending the tube round to form an elbow.

the next segment a sufficient length of tube to take hold of when we go to work upon it. When a sufficient number of lengths of flattened stem have been provided, we cut these up into segments of about 8 cm. in length; arrange them side by side after the manner of a palisade; and then with our

glass writing pencil rule two lines across the face of our tubes. The first of these lines ought to fall somewhere in the middle. It is to serve as a fiducial mark for filling in the blood from the finger. The second line, which may conveniently fall at a point to about $\frac{1}{2}$ or $\frac{3}{4}$ cm. to the end of the tube, is to serve as a fiducial mark in filling in the chemical agent whose effect we are to study.

The tube may now be used just as it is; or we may before using it furnish it with a siphon curve by bending it round at the level of our second fiducial mark. We do this by taking up each tube separately, holding it horizontally, and then passing it rapidly to and fro through a small by-pass flame. The action of gravity will then, as soon as the glass softens, bend round the tube for us (fig. 8, B).

Method of using the Emigration Tubes, and bringing the Chemotactic Agent into Application.

The emigration tube is first filled in up to the midway point with blood drawn from a puncture in the finger. In the case where we employ a bent tube this is done by letting the blood flow in through the siphon curve.

The chemotactic agent can now be brought into application in three different ways.

(1) *It may simply be superimposed upon the clotted blood.* This is done by using a *filiform pipette*, made by heating the stem of an ordinary capillary pipette in a small by-pass flame and drawing out, while with a rubber teat we apply internal pressure to prevent the walls of the hair-fine tube collapsing. Considered as a method for bringing a chemotactic agent into immediate application, this method falls short in the respect that the chemical has to diffuse down through the whole white clot before it comes into operation. In view of this, the method does not lend itself to the institution of any comparisons between normal blood and anæmic blood. For the experimental conditions are not comparable when our chemotactic agent has, in the one case, to diffuse through a length corresponding to half the column of blood; and, in the other case, through a length which may amount to nine-tenths of that column.

(2) The *second* method of bringing the chemical stimulus into application is that of *superimposing the chemotactic agent upon the unclotted blood* (fig. 9, B and C). Having filled in a curved emigration tube up to mid-point mark with blood, we tilt the tube so as to take in a dividing bubble of air; then fill it up as far as the elbow with the chemotactic agent; and then, after sealing up the distal

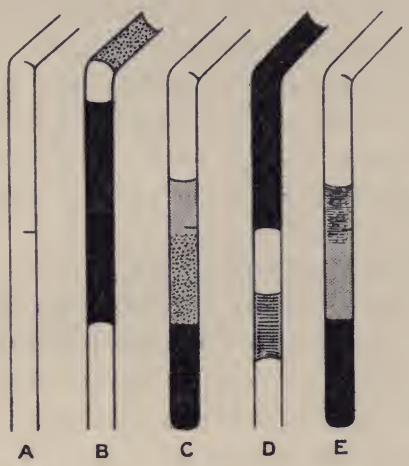


FIG. 9.

Method of adding chemotactic fluid to blood. A, curved emigration tube, empty. B, tube filled in with a column of blood, a dividing air bubble, and then, as far as the elbow, with a bacterial suspension. C, tube after centrifugalisation; the bottom of the tube is occupied by the red clot, and the intermediate portion by the white clot and the implanted bacteria; at the top is the watery menstruum in which the bacteria were suspended. D, tube filled in for *traversing;* in the lower portion of the capillary stem is the chemotactic agent; in the upper part the column of blood. E, tube after centrifugalisation; the bottom of the tube is occupied by the red clot, and the intermediate portion by the white clot, containing traces of the chemotactic agent; at the top the watery menstruum containing the bulk of this agent.

end of the tube, proceed to centrifuge. This method is applicable, in particular, when we are working with bacterial suspensions; for while the watery suspending fluid remains, by reason of its lighter specific gravity, on the top, the microbes are, by virtue of their higher specific gravity, carried down into the plasma to be embedded in the white clot all the way down to the leucocytic layer.

(3) The *third* method is the method of *traversing* (fig. 9, D and E). In employing this we may use either a straight or a bent emigration tube. We fill in, first, with our column of blood; follow on with the dividing bubble of air; and then, making use of the forerunning column of blood to serve as a brake, fill in up to the fiducial point with the chemotactic agent.[1] Finally, we seal up that end of the tube which has served as an inlet, and place the tube in the centrifuge.

Our chemotactic agent will now traverse the column of blood and take up a position at the top, leaving behind it in the plasma traces of whatever chemical it holds in solution. That this is what

[1] In practice the procedure of traversing is to be carried out exactly as here described. In the illustration, fig. 9, D, in order to convey the idea of traversing to the eye, the chemotactic agent precedes instead of following the column of blood.

actually happens can be shown by employing, in place of a colourless chemotactic agent, a solution of methylene blue, or simple water. This last, when it follows on after a column of blood and dissolves the red blood corpuscles which this leaves in its wake, will come out at the top coloured with hæmoglobin.

The traversing procedure will be applicable in the case where we want to bring into operation chemical agents, and especially applicable where we want to bring such agents into instant application.

When we are working with a series of tubes, as will practically always be the case, it will be well to place each, as soon as it is filled, into iced water or ordinary cold water. The buckets of the centrifuge will serve as convenient receptacles. After centrifugalisation the emigration tubes are placed in the incubator, according to circumstances, for from three to twelve hours or more. While in the incubator the tubes may conveniently be placed upright—that is, with the white clot uppermost—in plasticine. They may also be laid on their sides, tilted a little upwards. The inverted position is to be avoided; for when we invert our tubes we bring down into the white clot a shower of red corpuscles which block emigration and also obscure the view.

Method of bringing the Emigration Effect into View and taking Cognisance of the Results.

When all we want is to get a general idea of what is going on in the tubes, we can obtain this by introducing the unopened tube into an observation cell. A very simple form of observation cell can be made by placing small pellets of plasticine upon each of the four corners of a microscopic slide, covering in with another slide—allowing a little overlap—and then filling into the interspace either water or some more highly refractive fluid, such as glycerine or oil. By observing in such a cell we bring in view not only the leucocytes which have emigrated into the white clot, but also those which have escaped into the interspace which may develop between the clot and the walls of the capillary tube.[1]

[1] Attention may, in connexion with this, be called to facts which have an importance and a useful application in medicine, which happen to have also an importance and a useful application in connexion with the emigration method here under consideration. The facts I have in view are as follows: The blood of a person suffering from chilblains, or any other manifestation of a lowered blood coagulability, will, on centrifugalisation, generally fail to give the kind of white clot we require for our emigration experiments—that is, one that is firm and non-contractile. This condition of things can be remedied by the exhibition of calcium salts,

For all purposes of quantitative observations we blow out [1] our clots into water; wash carefully so as to remove leucocytes adhering to their exterior; and then mount them on a slide. We then, after cutting off the surplusage of red clot, fix by drying, and stain for a few minutes in Kühne's methylene blue freely diluted. The specimens are examined first, dry or in water, under a low-power objective, and afterwards in oil under an immersion.

or, as the case may be, by appropriate additions of these salts made to the blood when filling our capillary tubes. I would in connexion with this emphasise that we have here brought into clear view what is really the material factor in connexion with the effect exerted by calcium salts in the blood. And I may perhaps be permitted to point out, in connexion with my own work on calcium as an agent for promoting and citric acid as an agent for diminishing coagulability (*Brit. Med. Journ.*, July 29, 1893, and July, 1894; *Lancet*, January 18, 1896, and January 30, 1897), that while what I have said with reference to the clinical effects exerted has been, I believe, universally confirmed and accepted, what I have said with respect to the effects of the coagulability of blood *in vitro* has been traversed. This stands, as I believe, in relation to the fact that the laboratory workers who have repeated my work have employed methods which took into account rapidity, but left out of account firmness, of coagulation. It will now, I hope, by adopting the method of centrifugalising, and watching the effect exerted upon plasma which has been disembarrassed of corpuscles, be possible to arrive at unanimity in these matters. Finally, I may direct attention to the fact that what comes into view in centrifuged, is seen also in uncentrifuged blood. When we make to this appropriate additions of calcium salts we obtain, as I long ago pointed out, a firmer and non-contractile clot.

[1] This is done by the same technique as described in connexion with the *wet-wall method* (*see* p. 7).

General Considerations relating to the Movements of White Blood Corpuscles.

Before passing to consider the question how it will be possible to arrive at a quantitative expression for the leucocytic movements induced by a chemotactic agent, it will be well to take a general survey of the things that present themselves to view in every emigration tube.

We have to take into account in connexion with white blood corpuscles two kinds of movements. There is, on the one hand, a process of wandering at large; and, on the other hand, a directed movement—that is, a movement along some particular axis—undertaken under the direction of a chemical stimulus. We may call the first kind of movement an *eleutherotropic* movement. The second is usually known as a *chemotactic*—I prefer to call it a *chemotropic*—movement. It is, of course, the latter, not the former, kind of movement which we are here primarily concerned to study. For clearly it is the chemotactically directed movements of the leucocytes towards the bacterial focus, and not their

wanderings at large, which come into consideration in any conflict against infection.

None the less, a word may be said about *eleutherotropic movements*. One finds in every specimen of blood which has been simply centrifugalised and placed in an incubator, always a certain wandering at large of the leucocytes—in particular, the mononuclear white blood corpuscles, which have been tightly packed together by the action of the centrifuge, and are ranged at the top of the red clot, leave their ranks and wander out into the adjacent regions of the white clot. The polynuclear leucocytes also are affected by eleutherotropic wandering. They come out from the hinder ranks of the leucocytic layer, and also from deeper down in the red clot, and wander free. In our observations we leave out of account all those leucocytes that have wandered outside the white clot. We regard them as having run to waste.

A further point which claims attention in connexion with emigration is the *nature of the emigrating leucocytes*.

Ordinary *eleutherotropic emigration* is predominantly mononuclear, this being probably accounted for by the fact that the white blood corpuscles which are ranged up along the line which divides the red from the white clot are almost all mononuclear. In

chemotactic emigration we have either a differential emigration of polynuclear white corpuscles, or a mixed mononuclear and polynuclear emigration, in which either the one or the other of these varieties of leucocytes may predominate. In all such mixed emigrations the polynuclear, presumably because they are faster of foot, overtake the mononuclear leucocytes and pass on and occupy the more distal portion of the field of emigration.

Method of arriving at a Quantitative Expression respectively for "Compact" and "Dispersed" Emigration.

A quantitative expression for the emigration movement which takes place in a capillary tube can be arrived at in two ways. When we are dealing with a *compact* emigration (fig. 10, B)—that is, where the field of emigration is quite closely packed with leucocytes—we have simply to measure the area of that field, or (and this answers the purpose perfectly well) the length of clot occupied by the emigration; and we may conveniently measure it in terms of microscopic fields. In such measurements we take off from the base-line furnished by the distal border of the cone of leucocytes which occupies the base of the white clot. This

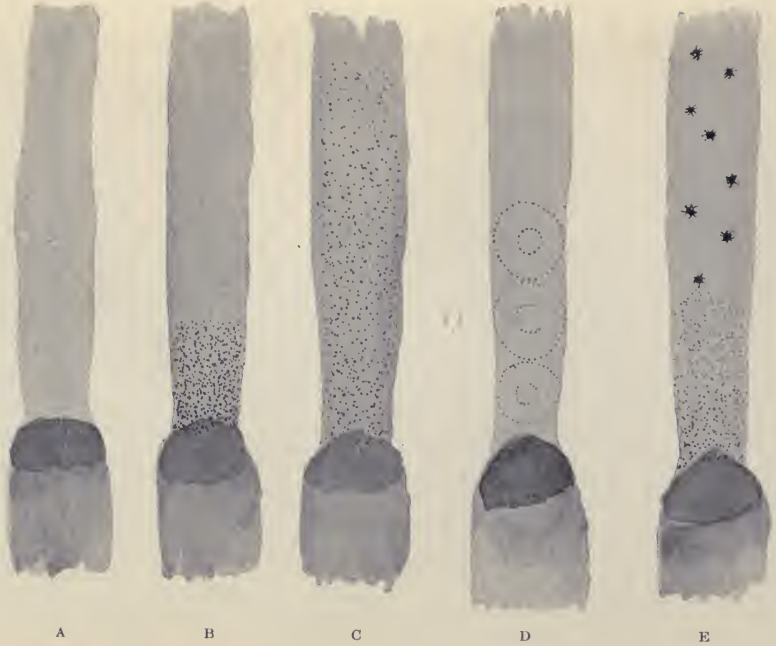


FIG. 10.

Clots from emigration tubes blown out and mounted. A, no emigration; B, compact emigration; C, dispersed emigration; D, method of dividing up the clot for purposes of enumeration; E, bacterial colonies coming up only in portion of clot which has not been reached by the emigrating leucocytes.

represents the original leucocytic layer converted, by the contraction of the fibrin, into a cap covering the upper end of the red clot.

When, as will happen when a longer time has been allowed for the wandering out and dispersion of the leucocytes, we have before us a *dispersed emigration* (fig. 10, c), it will no longer suffice simply to measure the distance the leucocytes have travelled into the clot. It now becomes necessary to enumerate the emigrating cells. Employing first a low-power lens, we bring the upper edge of the cap of leucocytes to the extreme edge of our field of view. Then turning to our oil immersion, we bring this down upon the central portion of the low-power field, and make a count of all the leucocytes which lie within its purview—when necessary helping ourselves out in our count by introducing into the diaphragm of our eyepiece a cover-glass divided up by light rulings, made with a glass writing pencil. Having obtained in this way a value for the emigration in an arbitrarily selected portion of the first microscopic field, we go back to our low-power objective and move our specimen along until the objects on the extreme distal margin have been carried right across the field, and now lie just out of view on the other side. The further steps in the procedure are now simple repetition.

What are obtained by this method of enumeration are, of course, only arbitrary figures, and it will be realised that the comparative values arrived at will be strictly accurate only where we are employing clots of similar thickness.

Survey of the Data which the Method has already given.

We may now pass on to consider some of the data that the method has already given. White blood corpuscles will move out in any direction towards a chemotactic substance. They will, however, emigrate more freely downwards than horizontally, and more freely horizontally than upwards.

Anaerobic conditions are more favourable to emigration than aerobic conditions. Leucocytes will travel out farther in the direction of a chemotactic substance when we absorb the oxygen in the tube with caustic alkali and pyrogallic acid and seal, than when we leave the end of the tube open to the air.

Leucocytes emigrate more abundantly in tubes standing at a temperature of 40° C. than in tubes standing at 37° C. They do not emigrate at temperatures of 10° to 15° C.—the temperatures which prevailed on our laboratory bench. After exposure to temperatures of 0° C. for periods of half to one hour they emigrate apparently as freely as before.

Emigration apparently goes on unaffected in the presence of ether. It is abolished or suspended in an atmosphere of chloroform.

Physiological salt solution—brought into applica-

tion either by traversing, or by superimposing it upon the clotted or unclotted blood — induces a very vigorous emigration of polynuclear white blood corpuscles. Weaker salt solutions induce a less vigorous emigration, and water again a less vigorous. Strong salt solutions—for example, 5 per cent. salt solutions—suppress emigration.

It will be appreciated in connexion with these and all findings obtained by this method that they do not tell us the effect of reagents acting in the specified dilutions directly upon leucocytes, but only the effect of these reagents operating from a distance. In other words, our experiments do not furnish information as to what would be the effect of bringing the chemical agents in the specified concentrations directly in relation with the capillary wall.

Bacterial suspensions which have been sterilised by heating evoke, according to the dilution in which they come into application, quite different effects. The general rule applying to bacterial suspensions would seem to be as follows : Concentrated suspensions usually completely suppress emigration. Ten or hundred fold diluted, they evoke vigorous emigration. When we employ progressively higher dilutions we arrive in time at a point when the effect is exactly the same as that of the particular fluid which we are employing as a diluent.

Normal bloods tested with one and the same series of bacterial suspensions exhibit quite different degrees of chemotropic sensibility. Chemotropic sensibility, not alone to bacterial suspensions but also to physiological salt solution, is very strikingly modified in the case of patients suffering from bacterial infections. This also applies to persons inoculated with streptococcic vaccines. In five out of six men, inoculated with such a vaccine and examined both before and afterwards, the emigrating response to streptococcus was very strikingly increased subsequently to inoculation. In the case of one man it was diminished.

Results somewhat similar to those obtained with dead cultures are obtained with suspensions of living microbes (streptococci and gas-phlegmon bacilli), but here the prolonging of the incubation period may strikingly alter the situation.

What generally happens may be summed up as follows: When, by superimposing and centrifuging, a heavy sowing of microbes has been implanted into the unclotted blood, the colonies come up all along the white clot, and emigration into this is completely checked. Where only a moderate implantation of microbes has been made we have in different parts of the clot different results: Bacterial colonies develop freely in the distal area of

the clot which is not invaded by emigration. In the intermediate region — that is, in the region where the microbes can grow out before the leucocytes arrive—one sees with the low-power objective areas specially crowded with leucocytes—these are in point of fact colonies which are being broken up and dispersed by invading leucocytes (fig. 11)—and with the oil immersion one sees that every leucocyte in these crowded masses is taking up microbes, and that there is also in all this region of the clot plentiful phagocytosis of scattered microbes (fig. 12). In the base of the white clot—that is, in the area where emigration has occurred earliest and most vigorously—one finds absolutely no trace of microbial growth.

The appearances which have just been described correspond, of course, to a period of conflict. This conflict is generally at its most interesting phase in tubes which have been incubated from three to six hours. When we come later—for instance, after twelve or more hours—the conflict is over. We then find either that the white corpuscles are masters of the field and the microbes have disappeared, or else that the microbes have invaded the whole clot, and that this crumbles away as soon as it is blown out into water. There can be little doubt that the crumbling away of the clot, and the

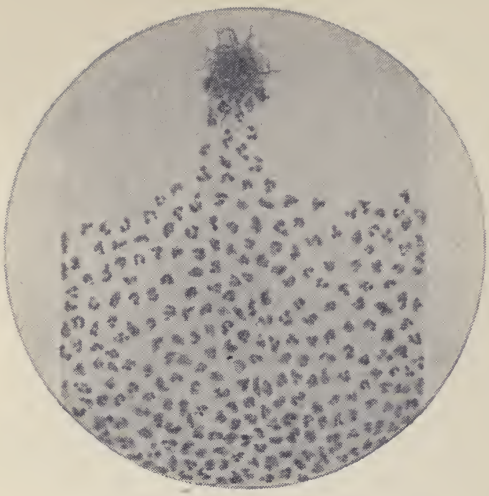


FIG. 11.

Extreme limit of emigration, showing phagocytes attacking streptococcus colony.

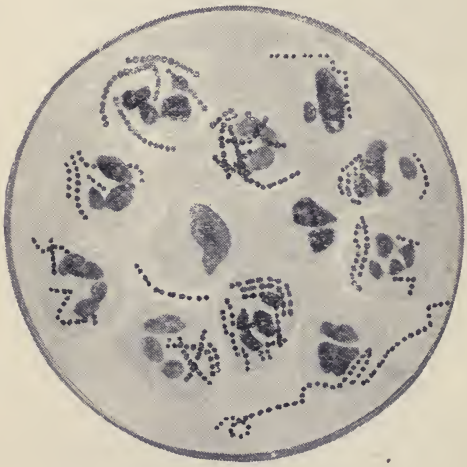


FIG. 12.

Phagocytosis of streptococci towards extreme limit of emigration.

Face p. 44.

overrunning of the blood with microbes, are due to the digestion of the fibrin, and to the corruption of the blood fluids by trypsin set free from the disintegrated leucocytes.

Experiments such as these just outlined, in which living microbes are brought into application on blood, provide, in point of fact, a valuable test method. They tell us the resultant of the *chemotropic sensibility* of the leucocytes, the *opsonic power* of the blood fluids, the *digestive capacity* of those phagocytes which come into action, and of the *antitryptic* and, where such comes into account, the *bactericidal* power of the blood fluids. We are, in fact, furnished with something like a complete evaluation of the antibacterial powers of the blood.[1]

There is still one element left out of account. The method here in question does not tell us anything as to whether or no there are bacterial poisons in solution in the blood fluids of the infected man. But this is a question which can be separately investigated. I have tried to find the

[1] It will be observed in connexion with tests thus conducted with centrifuged blood that, if we leave out of regard the centrifugalisation, they are in all essentials the same as the *phagocytobactericidal* tests with freshly drawn uncentrifuged blood which I have already described ("Vaccines and Drugs in Pneumonia," Constable, 1914).

answer by traversing normal bloods with sera derived from patients suffering from septicæmic infections. And I have by this procedure obtained in a series of cases what appeared to be a definitely chemotropic emigration.

All that has been recounted above is, of course, only a very small beginning. But I think we may be confident that the method for the study of emigration which has here been proposed will resolve important problems in connexion with infection generally, and also—and this is what specially concerns us here—some of the problems in connexion with wound infections which are now urgently pressing for a solution.

In the matter of general problems of infection it would, I think, be possible, by implanting bacteria into blood in combination with chemical agents which would respectively promote and hinder emigration, to resolve for each particular bacterial infection the question as to whether it is the leucocytes or the blood fluids which come most into consideration as destructive agencies. That problem once resolved, we should know whether we ought, in the infection in question, to direct our chief efforts to increasing the efficacy of the blood fluids or to modifying the chemotropic sensibility of the leucocytes and encouraging emigration.

Again it looks as if it might be possible by very simple experiments to resolve the problem as to why in gonorrhœa, and also in other surface infections, the purulent discharge is suddenly arrested when the microbes succeed in invading the blood-stream, or establishing themselves in an articulation or elsewhere in the interior of the body. It would seem possible (for something of this kind would seem to occur in septicæmias supervening on wound infections) that we may be dealing here with a paralysis of the emigrating powers of the leucocytes. Or, again, it is possible that in these cases emigration may be simply suspended by a redistribution of the chemotactic forces. In other words, the cessation of the external discharge may simply mean that there is now in the blood a bacterial poison; and that this chemotactic element, acting upon the leucocytes as a *vis a tergo*, counterbalances the *vis a fronte* of the chemotactic substances produced by the bacteria on the external surfaces.

In connexion with the particular problems of wound infections we may hope at no distant date to come into possession of information which will enable us to activate or restrain, according as the one or the other may approve itself the better policy, the emigration of leucocytes into the wound. And we may hope also to determine in connexion

with every antiseptic or other solution which is brought into application in a wound, whether it promotes or hinders emigration.

Finally, let me point out—for everything that concerns bacterial vaccines concerns the treatment of wound infections—that experiments on emigration will almost certainly resolve a number of important outstanding questions in connexion with vaccines. They ought very easily to resolve the question as to what is the best excipient for a vaccine — whether a menstruum which would restrain emigration, or one, like physiological salt solution, which would call forth a vigorous emigrating response at the point of injection. And lastly —and this would be one of the most important applications of observations on emigration — we ought to be able to determine what is, in the case of each bacterial vaccine, the dose which will induce the earliest possible and the most effective determination of phagocytes to the focus or foci of infection.

CHAPTER III.

Treatment of Wound Infections.

We may, with such new knowledge as we have acquired from the experimental methods I have described, now revert to the consideration of those three ways of combating wound infections enumerated earlier in this discourse. It will be remembered that these were: *Treatment by Antiseptics*, *Treatment by Physiological Methods*, and *Vaccine Therapy*. We will take them one by one.

(I) Treatment by Antiseptics.

If we adopted the Socratic method, and were to inquire of the first man we found engaged in washing out a wound what were the grounds for his confidence in the utility of the procedure, he would probably make some such answer as the following: "I know that the antiseptics which I am bringing into application are agents which directly kill and inhibit the growth of microbes. There is no other agency known which would be

competent to do the bactericidal work that these antiseptics do in the wound. And, again, it is everybody's knowledge that Lister, by introducing his antiseptic treatment, extirpated those septic infections of wounds which before the advent of his method devastated the surgical wards of every hospital."

And if we were to push our question further, and ask of the surgeon to what particular end and object his procedures were directed — whether it was the sterilisation of the wound; or the killing off of a large proportion of the microbes, or the imposition of a check upon the survivors; and if we were further to ask, whether the particular antiseptic in the particular strength in which he was employing it could be relied upon to achieve the end in view; we should probably be told that, supposing that the antiseptic did not completely sterilise the wound, it would inevitably kill a large number of microbes; and it would probably also inhibit the growth of any survivors. And, inasmuch as one or other of these objects would be sure to be achieved, there could be no question but that advantage would accrue to the patient.

We should, in short, get an answer which proceeded upon at least one erroneous assumption, and which betrayed loose and inconsequent think-

ing, and a reluctance to come to close quarters with the question. But the reasonings of the larger part of humanity are neither better nor worse than this; it is not for that less necessary to take them into very serious account, and to do our best to correct them when they mislead.

Let us begin, since Lister is the fount and origin of all antiseptic treatment, with what relates to his work. Lister's name is associated with two discoveries. The *first* of these is the discovery that we can, by an *anticipative prophylactic application*, hold off microbes from surgical wounds, and so avoid wound infections. The *second* is that in cases of compound fracture where the wound is already infected we can still, by what I may perhaps call a *retrospective prophylactic application of antiseptics*, stave off the wound infection. The first of these is a discovery of absolutely universal application, and it will carry the name of Lister down to remotest posterity. The second discovery has reference only to a particular kind of traumatic wound, and shows that prophylactic applications of antiseptics can be usefully employed also in connexion with some wounds which are already infected.

It is clear that neither of these discoveries finds any direct application either in connexion with

prophylaxis or the treatment of the infections which occur in projectile wounds.

What it is necessary to say on the possibility of preventing septic infection by sterilising projectile wounds can be said in a very few words. The principle that microbes can be held off from wounds by an antecedent employment of antiseptics has no application to projectile wounds, for these are infected before they are seen by the surgeon. Nor, again, is the Listerian discovery that prophylactic applications of antiseptics in the ordinary compound fractures of civil life can stave off wound infection related to conditions such as obtain in projectile wounds. Retrospective, or, as we may also call them, *ex post facto* prophylactic applications of antiseptics will give good results only when the microbes are accessible. In the case of the ordinary compound fracture of civil life this is often the case. For here the microbes lie exposed on the external surface of the bone which has been thrust through the skin. The contrary holds for projectile wounds. Here the microbes are inaccessible. They have been carried down deep into the tissues, and lie on the inner face of a torn and ragged track; and that track is blocked by blood-clot and hernia of muscle.

It is clear that the utmost that prophylactic

applications of an antiseptic could under such conditions achieve would be an incomplete sterilisation. And an incomplete sterilisation would leave us with a wound infection, and in a few days with as bad an infection as before.

Coming now to actually subsisting wound infections, we see that exactly the same thing would apply. We are not entitled to infer from the fact that the method of Lister is within its limitations an effective method of prophylaxis that it is also an effective method of treatment. That is clearly a question which must be determined as an independent issue.

When we approach the question in this way we see that the first point which has to be determined is: What particular concentration of each particular antiseptic will, when applied to the wound, exert there a bactericidal action on the microbes? In connexion with this we must beware of the fallacy of taking the figures for an antiseptic acting on microbes in watery suspension and seeing in these an all-round formula of efficacy for that particular antiseptic.

A formula of efficacy of this kind might, of course, find a useful application where the sterilisation of skin surfaces and instruments was concerned. For here the antiseptic comes into operation on

exposed microbes in full strength. In practically every other case the conditions would be entirely different. The antiseptic would have to come into operation in a medium which quenches its anti-bacterial action.

I have recently, in dealing with internal medication by antiseptics in pneumonia, brought forward[1] an array of experiments which show that the quenching of the anti-bacterial power of antiseptics by the medium in which these come into application, is the essentially important factor to be considered in connexion with their medicinal use. In particular I have shown in connexion with drugs like lysol, creosote, and guaiacol, that doses which would almost certainly be lethal would have to be administered before these antiseptics could come into operation in blood.

The same sort of thing holds true of pus. But here the situation will be different in two respects. It will be different in respect that, as compared with serum, pus exerts a greater quenching effect upon antiseptics. It is, if I may put it so, more *antiseptico-tropic*. This will prevent us taking the antiseptico-tropic values for the serum and applying them to the pus in the wound. Again, the con-

[1] "Drugs and Vaccines in Pneumonia," Constable, 1914.

ditions under which an antiseptic comes into application in a wound will contrast with those which come into application in internal medication. In connexion with internal medication we have to take into consideration the quenching influence which would be exerted by the totality of blood. In applying antiseptics to the wound it lies with us to make the conditions much more favourable to the antiseptic. We can, if it is a question of washing out a wound with antiseptics, make the relation of antiseptics to pus anything that we please. And where it is a question of leaving an antiseptic behind in the wound for the purpose of inhibiting growth, we can also, within limits, lay down our own conditions, and make provisions which will prevent the conditions becoming too unfavourable to the antiseptic.

If there are, in the published literature on antiseptics, any papers dealing with the investigation of the efficacy of antiseptics from this point of view, they have escaped my observation. I have accordingly, in conjunction with my fellow-workers, Dr. W. Parry Morgan and Dr. A. Fleming, set to work to supply the missing data. To find out what concentrations of antiseptic ought to be brought into operation in washing out a wound we took nine volumes of antiseptic to one of pus. To

determine what inhibitory effect would be exerted by an antiseptic left behind in a wound we took one portion of the antiseptic to—as the case might be —two or four volumes of pus. It will be seen that by this plan of operation we conduct our experiments directly on the microbes and pus furnished by the wound; in other words, instead of dealing with any abstract issue, we deal with the concrete question which presents itself in the particular wound infection which happens to lie before us.

The general results obtained in this investigation will be separately set forth. At the moment it will suffice to call attention to the fact that when employing nine volumes of the antiseptic solution to one of pus from the infected wound, and leaving the antiseptic in application for ten minutes, a strength of 1 in 40 of carbolic acid, and strengths of 1 in 400 of biniodide of mercury, and 1 in 500 of tincture of iodine all failed to sterilise. Again, in experiments on inhibition, one volume of a 1 in 30 dilution of lysol, and 1 in 400 of tincture of iodine, and 1 in 200 solution of biniodide of mercury did not avail to prevent bacterial growth in four volumes of pus. But I must not delay over the question as to what will with a particular antiseptic be the particular concentration required for the attainment of a particular antibacterial effect. Let

us revert to our task of trying to bring the whole question of the employment of antiseptics in wounds into some sort of proper perspective. It will help us to do this if we consider the following questions:—

(1) *Is there any reasonable prospect of sterilising the wound by an application of antiseptics?*

So far as the pus which is brought into intimate contact with the antiseptic is concerned, it would probably be possible to sterilise this by methods which will elsewhere be explained. But we have in the wound not only pus which can be reached by our antiseptic washings but also pus which is locked up out of reach in blind alleys and pockets. And, again, we have in the infected wound not only a microbic infection of discharges, but also a microbic infection of the granulation tissue. And assuredly the really formidable difficulty in connexion with the sterilisation of the wound is that of getting sufficient penetrating power to deal with these sheltered microbes.

Now the ordinary antiseptics which we employ in wounds have as good as no penetrative power, and, though it is possible to undertake comparative experiments, and as an interesting academic exercise to determine for a series of antiseptics how far their antibacterial influence may extend in agar or any

other artificial medium, academic exercises like this ought not to divert our attention from the fact that there is not, among all the competing antiseptics, one which can penetrate into and sterilise the walls of an infected wound. In fact, if ever an antiseptic sterilised a heavily infected wound, that would well deserve to be announced in all the evening and morning newspapers. Nor is it matter for surprise that antiseptics should not be able to penetrate into granulation tissue. Let us call to mind the fact that this is composed of continuous layers of cells; that the cell wall is a quasi-impenetrable membrane; further, that we have in the granulation tissue a well-developed system of capillaries, capable of absorbing and carrying away any antiseptic that might penetrate; and, lastly, that we have also in the granulation tissue an outflowing lymph current. Having realised the inefficacy of antiseptics for the purpose of sterilising an infected wound, let us now pass to the next question. It may be formulated thus:—

(2) *Is there, in point of fact, any ground for the confident belief that a reduction in the number of microbes, such as would be obtained by washing out the wound with antiseptics, must carry advantage to the patient?*

We have realised that it is a firmly established conviction that every procedure which leaves behind in the wound fewer microbes would, like a smaller sowing of seed, sensibly reduce the ultimate crop, and so sensibly advantage the patient. The bacteriologist does not see in this a matter of course. He thinks not only of the sowing, but of the soil. He reflects that when we are dealing with a microbe which reproduces itself rapidly on a particular medium—let us say the typhoid bacillus in peptone broth—the lightness or heaviness of the sowing would after the lapse of a comparatively short time hardly come into account. Again, in the case of a microbe which multiplied itself very slowly in a particular medium the sowing would, unless the incubation period were indefinitely extended, make very little difference to the result. Finally, where a microbe grows very slowly on a particular medium, but very rapidly as soon as this undergoes transformation, the population of microbes found in the culture would clearly depend less on the number implanted than on the time taken to convert the nutrient substratum from a bad into a good cultivation medium. It is, in the light of what has gone before, quite easy to see the application of this to the wound. Whether few or many serophytic microbes are left behind in the

wound will make comparatively little difference to the number found in the uncorrupted lymph. For serophytes will multiply rapidly unless constantly kept down by phagocytosis. Again, in the same way, whether few or many sero-saprophytes are left behind would not make much difference to the number found in the uncorrupted discharge. For sero-saprophytes grow very badly on this medium. But the factor which will readily exercise a determining influence on the result will be the rate at which the lymph becomes corrupted. And the practical conclusion emerges that what is really difficult in dealing with an infected wound is not to thin out the microbes, but afterwards to keep down their numbers. We are here carried along by our train of thought to the "dressing of the wound"; and in connexion with this we may put the following question to ourselves:—

(3) *What conclusions can be drawn from the fact that frequent re-dressings are indispensable in connexion with the treatment of infected wounds by antiseptics?*

This is one of those questions of which we realise the fundamental significance as soon as they formulate themselves in the mind. When our treatment has miscarried, and the wound has filled up

again with pus, and this has become tryptic and has begun to digest the granulations and skin surfaces with which it comes into contact and when bacterial poisons are being absorbed into the system, we are compelled to re-dress the wound. In other words, when we have been falling away we have to try to get back to the position which was reached at the previous dressing. And let us in this connexion note that it is one thing when unsuccessful to fall back upon dressing, and to make of this a point of departure for trying a new way; and quite another thing to accept dressing as a necessary and inevitable element in our programme of treatment, and then not even to propose to make it a point of departure for a new therapeutic effort, but calmly to contemplate an everlastingly repeated setting out into a blind alley, and an everlastingly repeated return to our point from which we started. If grace had been given us to see things with unsophisticated vision, it would be clear to us that to make constant re-dressing an integral and indispensable element in our programme of treatment is really as much of a confession of failure in the case of an infected wound as in a surgical operation. It is equivalent to saying that our method of treatment leaves the wound in a condition which makes healing impossible. And this leads on directly to the question :—

(4) *How are we, in view of all the above, to account for confidence in the utility of the antiseptic method of treatment?*

We may here begin by emphasising that in all probability the antiseptic method, considered as a method for preventing the importation of foreign germs into the wound, has deserved everything in the way of praise that may have been said of it. For it is no doubt owing to the fact that antiseptic solutions have everywhere been employed for washing out the wounds, that there have not developed in the military hospitals in this war any of those graver forms of infection which in pre-Listerian days never failed to put in an appearance. When, however, we pass from prophylaxis to treatment, and from the consideration of the effects in connexion with the patients, taken as an aggregate, to the effects which manifest themselves in the individual who is under treatment, it is then that we come face to face with the problem as to how it has come about that the obvious non-success of the antiseptic treatment is not generally appreciated. It seems to me that this also must be put down to sophisticated vision and to the effects of education. We must remember that the practitioner of to-day has been educated to expect to find, within a few hours after washing out an infected wound with

antiseptic, as much pus and as many microbes as when he last came to dress it.

Finally we may ask ourselves one more question.

(5) *Is it possible that applications of antiseptics may ever do harm?*

In dealing with this question we must send adrift that verbal formula "injury to tissues," which meets the eye everywhere in surgical literature. And we must realize that so long as we talk only of an undefined injury to undefined tissues we shall never make any progress. Precise answers can come only from precise questions.

We ought here to ask ourselves in connexion with particular concentrations of particular antiseptics (*a*) whether they hinder or promote, to the disadvantage of the patient, the emigration of leucocytes; (*b*) whether they paralyse their phagocytic activity; (*c*) whether they favour the "corruption of the lymph"; and (*d*) whether they stimulate microbial growth. I hope in future to deal with all these questions. For the moment let it suffice to say that antiseptics in various dilutions can do all these things; and to emphasise the following. An addition of carbolic acid may, as shown by my fellow-worker, Dr. W. Parry Morgan, diminish the antitryptic power of the serum. And it has long

been known that antiseptics in high dilutions—dilutions which will be temporarily realised when antiseptics are left in the wound—powerfully stimulate microbial growth. This has, by my fellow-worker, Dr. A. Fleming, recently been demonstrated to the eye by implanting the *Bacillus aerogenes capsulatus* of Welch into nutrient media which had received graduated additions of antiseptics, and using the amount of gas formed as a measure of microbial growth.

We now pass to—

(II) Treatment by Physiological Methods.

We shall do well to begin by putting quite away from us the current preconception that to abandon antiseptics would be equivalent to abandoning the programme of killing microbes in the wound. A moment's reflection will show that Nature has from the very beginning of things been bringing to bear her own antibacterial agents on infecting microbes; and that we have in antiseptics merely a recent substitute for these. Moreover, the surgeon, in treating wounds, has all along, though not with conscious aim, been bringing the antibacterial agencies of the body to bear on the infecting microbes.

In treating a wound infection by physiological methods we have therefore only to follow the surgeon's lead. But we may hope, as we go along, to improve upon his methods. For we shall fix our attention on the guiding principle which he has missed.

The chief points which the surgeon has insisted upon in connexion with the treatment of infected wounds and tissues are the following: Where there is an abscess sac or a closed cavity containing pus, this must be laid open, and an outlet for the discharge must be provided—if possible in the most dependent part. Where an infection has spread diffusely in the tissues, free incisions must be made; and where these incisions pass through infiltrated tissues they must be carried from sound skin to sound skin, and all the way down to the healthy structures underneath, and here hot fomentations should afterwards be applied. Lastly—and this is one of the teachings of the present war—when amputating through infected tissues unrestricted drainage must be provided: either by leaving the wound unsutured, or (in cases of gas phlegmon) by reverting to the mediæval method reintroduced by Fitzmaurice Kelly, of cutting the limb squarely across, and dispensing entirely with flaps.[1]

[1] *Lancet*, January 2, 1915, p. 15.

Let me now try to show you that all these procedures—and it will not be necessary to consider them all in detail—will in the ordinary case bring the antibacterial agencies of the body into play. And let me further try to show you that when they fail to do this satisfactorily, they never, even when they accomplish all that the surgeon asks, do any effective good in combating the infection.

I shall begin by considering the *rationale* of opening up the abscess sac. The popular explanation accounts for the utility of this procedure by telling us that it provides issue for the infected discharges. But that is quite inadequate. For not only does the operation provide issue for the infected discharges, but when it succeeds it brings about the destruction of the microbes which are embedded in the walls of the abscess sac. In reality it alters the whole situation. In the unopened abscess the antibacterial agencies of the body are overborne by the mass effect of the infecting microbes. The white blood corpuscles in the abscess sac are paralysed, or killed; and all the antibacterial power of the lymph has been lost. In the abscess that has been laid open and emptied, the infected bacteria are overborne by the mass effect exerted by the antibacterial agencies of the body. Fresh antibacterial lymph is streaming in through the walls;

and phagocytically active leucocytes are emigrating into the empty cavity. But for all that the infecting bacteria are overborne, the infection is not necessarily extinguished. The laying open of the abscess does not always put everything right. The mechanical conditions may leave much to be desired. It may be necessary to obtain a larger outpouring of lymph to wash the embedded bacteria out of the walls of the wound, and to prevent them accumulating in the abscess cavity and effluent channel. Again, the antibacterial agencies of the body may require to be brought into more effective operation. It may be desirable to bring to bear on the microbes both a greater volume of antibacterial lymph and a larger force of phagocytes; or it may be proper to repress the emigration of leucocytes so as to prevent any breaking down of these in the wound.

Now the supplementary surgical procedures which were enumerated above, all contribute, more or less effectively, to the accomplishment of one or other of these ends.

Drainage-tubes are devices for preventing the accumulation of infected discharges. But they do not really keep down bacterial growth in the walls of the abscess cavity. There ought to flow out from a wound not a pus composed of disintegrated

leucocytes and microbes, but a lymph which is inimical to microbes, and favourable to phagocytic activity; and things do not begin to clear up in a wound till its effluent runs clear.

Free incisions carried down into infiltrated tissues are intended to furnish an ample outlet. But in reality the dimensions of the outlet do not necessarily correspond to the superficial area of the incisions. In point of fact the effective outlet will in infiltrated tissues correspond only to a small section of that area. For the lymph spaces are blocked with leucocytes and fibrinous exudation. And there will, moreover, ooze out from the cut surfaces a highly coagulable lymph, which very quickly seals up any open pores.

Hot fomentations, in addition to macerating and bringing away the inflammatory exudate, will induce active hyperæmia, and so increase the outflow of lymph.

Leaving operation wounds unsutured and dispensing with flaps will, as already explained, give unrestricted drainage—so far at least as the mechanical conditions are concerned.

We have now arrived at some sort of a general idea as to what would be embraced under the term "Treatment by Physiological Methods," and we have realised that the empirical procedures of the

surgeon furnish us with something to work with and improve upon.

It will be taking a first step to the improvement of these methods if we draw up for ourselves a complete list of desiderata. We shall, in setting these out, have to bring them into relation with the actual types of wound infection which come up for treatment.

In reality our infected wounds conform, nearly all of them, to one or other of two types: In the *first* type we have an infection of either the unclothed internal surface of the wound, or of the granulation tissue lining it. Examples of this type of infection are furnished (*a*) by recent projectile wounds whose walls are implanted with microbes; (*b*) by suppurating cavities which have just been opened up and evacuated; and (*c*) by old-standing suppurating wounds which have just been washed out and left clean. In our *second* type of wound we have an infection in a dry and infiltrated wall of an infected cavity and in the tissues contiguous to this.

In the former type of wound infection it would be a desideratum to wash the infecting microbes out of the walls of the wound by means of a powerful outgoing current of lymph; and it would be desirable in connexion with this lymph that it

should carry in with it into the infected cavity whatever force of phagocytes might be required; that it should furnish a favourable medium for, and directly assist, phagocytosis; that it should repress bacterial growth; and that it should not suffer any sensible diminution of antitryptic power if, after ineffective phagocytosis, a certain number of leucocytes broke down in it.

In the second type of infection, while everything that applies to the first type would apply, it would probably be desirable, as special measures, to repress further emigration of leucocytes, and to render the lymph incoagulable so as to prevent any stanching of the lymph outflow.

For the complete realisation of these desiderata we should require to have at disposal an agency for powerfully increasing the outflow of lymph. (I propose almost immediately to show that we have this at disposal.) Further, it would probably be necessary to have at disposal—but till further research has been carried out it is impossible to speak with certainty on this subject—means for promoting and repressing emigration. And lastly, it would almost certainly be necessary to be in a position to increase at need not only the antibacterial power of the lymph with respect to the infecting microbes, but also its general power of repressing the growth of

sero-saprophytes. This, however, will come up for consideration in connexion with treatment by vaccine therapy.

As just announced, I pass now to consider what agents we have at disposal for increasing the outflow of lymph. In this connexion we have already seen that the lymph flow from the wound can be increased by the application of hot fomentations. It can be increased also by introducing ether into the wound—the ether, like the hot fomentations, no doubt acting by inducing active hyperæmia.

But I think that better than either of these, because it is more continuous in its action, and because it renders the lymph incoagulable, and also perhaps because it represses emigration, is the lymphagogic application which I have been recommending now these many years back. This consists of a 5 per cent. solution of common salt, mixed with ½ per cent. of sodium citrate. This brings into play osmotic forces, and "draws" the lymph out of the walls of the wound by a *vis a fronte*. The sodium citrate is added with a view to decalcifying the outflowing lymph and rendering it incoagulable.

I may perhaps be allowed to say with regard to this lymphagogic solution—or, rather, with regard to the simple 5 per cent. salt solution, which I find works in most cases equally well—that it has in

this war proved itself pre-eminently useful. When brought into action upon a dry and infiltrated wound, or a wound that is foul and covered with slough, it resolves the induration, brings back moisture to the surfaces, and cleans up the wound in a way that no other agent does. Applied in gaseous gangrene in the form of a wet dressing to incisions which have been carried down into infected tissues it causes lymph to pour out of the wounds, and arrests the spread of the infection. And, again, applied in gaseous gangrene to an amputated stump in cases where it has been necessary to leave infected tissues behind, it reverses the lymph-stream and draws out the infected lymph—saving life in almost desperate conditions.

What would be the proper culmination and end to the treatment of wound infections by physiological methods?

We have now arrived at a point when it will be proper to keep our eyes somewhat less closely upon the ground, and to ask ourselves what kind of a coping-stone is to be placed upon our edifice of physiological treatment. For it is clearly unthinkable in connexion with such treatment carried out on scientific lines that it should lead to nothing better than to that everlasting dressing and re-

dressing of the wound which all antiseptic treatment seems to consist of. I am convinced that, when once we shall have learned exactly how to regulate the outflow of lymph, and to control emigration and phagocytosis, it will be practical policy to make an end, once and for all, to a wound infection, and to close up the wound.

Even as we stand at present that seems to me to be to some extent a realisable ideal. While it would lead too far to follow up this question in detail, it will, perhaps, not be amiss to direct attention to the following points :—

It will always and ever be impossible to sterilise a wound within the space of a few minutes. To wash out microbes from the granulation tissue will always take time. And we shall always have to allow time for the leucocyte to find the microbe; and for phagocytosis; and for the digestion of the microbe in the interior of the phagocyte. And again, and above all, we shall always have to allow a very large margin of time for the miscarrying of lymph lavage, emigration, phagocytosis, and the intracellular destruction of the microbes, and for the necessary going back over all these processes.

In view of this it will be clear that when we embark upon physiological treatment we ought to carry it out unremittingly. And our treatment will

perhaps best take the form of continuous irrigation or continuous baths.

When by these means we think we have rendered our wound sterile, or nearly sterile, we must, in closing up the wound, or in giving it an opportunity of healing up under a scab, always proceed by the method of trial and error and provide for the possibility of the microbes again assuming the upper hand.

(III) Treatment by Vaccine Therapy.

I emphasised at the outset of this discourse that treatment by vaccine therapy could take rank only as ancillary to treatment by physiological methods. In *Treatment by Physiological Methods* we take the antibacterial agencies of the patient just as they are, and do our best to bring them into more effective application on the infective microbes. In *Vaccine Therapy* we seek to reinforce those agencies. We endeavour to increase the bacteriotropic power of the blood, and to modify the chemotropic sensibility of the leucocytes. And, now that we have come to appreciate its importance, we should seek to increase also the antitryptic power of the blood fluids.

Let us try to see how the case for vaccines and vaccine-therapy stands, keeping always before us

the great practical issue as to how much clinical benefit can in the particular case be secured for the patient, and arranging, for the purposes of our survey, the manifold applications of vaccines under six subheadings.

(1) *Prophylactic Employment of Vaccines.*—This is not only from the theoretical point of view the best of all methods of employing vaccines, but it is also the method which gives, in practice, the maximum of advantage. We have only to look to the results obtained by prophylactic vaccination against small-pox, cholera, plague, and typhoid fever.

(2) *Employment of Vaccines in the Treatment of Localised Bacterial Inroads.*—Next to prophylactic inoculations, this gives the best results. And the results, in respect of their being almost immediately manifest to the eye, are even more dramatic than those of any preventive inoculation. Perhaps the most rapid and convincing results are those obtained by small doses of streptococcic vaccine in lymphangitis and erysipelas; by staphylococcic vaccine in furunculosis, when the boil is just beginning to develop; and by minimal doses of tuberculin in phlyctenular affections of the conjunctiva.

(3) *Employment of Vaccines in dealing with Unopened Abscesses and other Localised Infections*

where the Microbes cannot be reached from the Blood-stream.—Vaccines are here, so far as appears to clinical inspection, quite inoperative.

(4) *Employment of Vaccines in the Treatment of Localised Infections associated with heavy Auto-inoculations.*—The scientific application of vaccines in these cases is extremely difficult and laborious, and the results which are obtained — and those obtained in the treatment of developed phthisis by tuberculin supply a good example — are not very convincing.

(5) *Employment of Vaccines in the Treatment of Undrained Wounds infected by Sero-saprophytes.*— There is not yet a sufficient body of experience to decide the question as to whether benefit can be obtained from vaccines in these cases. The question will be further discussed below in connexion with the wound infections of the war.

(6) *Employment of Vaccines in the Treatment of Septicæmic Infections, and, in particular, Streptococcic Septicæmias.* — Up to the present—except perhaps in certain series of experiments relating to typhoid fever — vaccines have, on the whole, given, in septicæmias, very disappointing results. But it will be obvious on consideration, that as we advance through the whole series of applications —from prophylactic application to the employment

of vaccines in septicæmias—the conditions are becoming progressively more difficult; so that success in treatment of septicæmias, if it is ever attained, will be the very final achievement of vaccine therapy.

We have now prepared the ground for considering what has been obtained by the use of vaccines in the treatment of wound infections in this war.

I have, in connexion with this, heard the opinion of a very distinguished French surgeon—pronounced after watching the effect of vaccines upon, I should think, undrained wounds and septicæmic infections —that they had never done any good. I shall, by my general survey above, at least have put you on your guard against generalising from one class of cases to all other cases. Let us now take each class of case separately, and ask ourselves whether, in this, vaccines have rendered any service. I think we shall then see that things work out everywhere in accordance with scientific law.

(1) *Prophylactic Inoculations of "Antisepsis Vaccines."* — If prophylactic inoculations of this kind have not been undertaken in our army it has not been because a supply of antisepsis vaccines has not been at hand, but because the idea of undertaking such inoculations has not appealed to the individual medical officers who have given first aid to the wounded. And if any prophylactic

inoculations have been undertaken, this can have been only on a very small scale; and the fact has not transpired. To be considered therefore here is only the question as to what we should on a priori grounds be justified in expecting from prophylactic inoculations against wound infections, undertaken upon the wounded. The answer is, I think, not doubtful. We might justifiably hope, in a proportion of cases, to sterilise the upper reaches of the wound which would be less heavily implanted; and perhaps in isolated cases—those in which we have a comparatively light sowing of microbes—to sterilise the whole wound. Moreover, if we could employ vaccines in combination with *physiological drainage* (I mean, by that, free out-pouring of lymph obtained by the use of a lymphagogic solution) we might, I think, hope to stave off infection in a fairly large proportion of cases. But—and I have already, though perhaps not emphatically enough, drawn your attention to this in connexion with prophylactic applications of antiseptics — it will, when we set out to sterilise a wound, nearly always be a question of achieving either all we want or nothing. To leave behind, especially in the upper reaches of a wound, a few microbes, which immediately set to work and multiply, amounts, from the point of view of the future of the wound, to

exactly the same as leaving behind alive the whole original population. If one really intends a war of extermination there must be no remissions; and if our first effort with vaccines and physiological drainage fails, we must immediately follow up with further efforts.

(2) *Employment of "Antisepsis Vaccines" in Cases where the Microbes make an Irruption into the neighbouring Tissues.*—In connexion with projectile wounds it is not very uncommon to see the infecting microbes breaking bounds, and making an irruption into the neighbouring tissues. This will occur either in a wound which has not been laid open, or where the lymph flow has stanched, and the microbes have been imprisoned in an infiltrated wall. The bacterial irruption may follow the course of the lymphatics as a lymphangitis; or it may take the form of an erysipelas or cellulitis. In these forms of infection occurring in connexion with projectile wounds, vaccines give exactly the same dramatic effects as in the small wounds of civil life —the only difference being that, when the irruption has been beaten back, we have in the case of projectile wounds still the original focus of infection to deal with; and have, unless we improve the condition of the wound, always to be upon our guard against a renewal of the irruption.

(3) *Employment of "Antisepsis Vaccines" in connexion with well-drained Wounds.*—When we have in a wound quite unobstructed mechanical drainage—such, for instance, as is provided by amputation without flaps—we have, from the point of view of the immunologist, conditions exactly parallel to those which obtain when microbes make a first irruption into healthy tissues. In other words, we have here—and probably also where we have good physiological drainage—brought to bear upon the microbes an ample force of phagocytes in conjunction with a rapid, percolating or outflowing, as the case may be, stream of lymph. As a consequence, vaccines give in these cases results which are so strikingly favourable as to arrest the attention of every beholder.

(4) *Employment of "Antisepsis Vaccines" in imperfectly drained Wounds.*—An overwhelming proportion of projectile wounds which are under treatment in hospital would, regarded from the point of view of the mechanical conditions, come into the category of imperfectly drained wounds. And this is as it must be. The conservation of the wounded limb is clearly the first object of the surgeon; and the treatment of the bacterial infection is quite subordinate. For example, no one could ask that a leg which had been perforated by a

bullet should be cut free from all its attachments to give better drainage to the infected track.

Now it might be legitimate to say that these undrained wounds were analogous to the unopened abscesses referred to above, were it not that this comparison would do much less than justice to the difficulties which confront the immunisator in the wound where pus accumulates. Not only have we in the recesses and backwaters of such a wound conditions which make it impossible for the anti-bacterial agencies of the body to establish by their mass effect a position of superiority over the microbes; but we have in the corrupted discharges and the multiform bacterial growth which they harbour, obstacles to successful immunisation such as are never encountered in an unopened abscess cavity. It is therefore not to be expected that we should in these cases see—and in point of fact we do not see—after the exhibition of vaccines any diminution in the pus which pours from the wound.

None the less we shall do well carefully to consider certain questions in connexion with the employment of vaccines in the treatment of imperfectly drained wounds. It is clearly a matter for consideration whether—despite the fact that the output of pus from the wound is not diminished—there may not be some useful clinical result

from the vaccines. It is quite likely that there is such an effect; and that it takes the form of a "nibbling" at the infection in those parts of the wound lying above the ground level of the pus; a better entrenchment against the microbes; and, behind this, a massing of reserves which would be brought to bear if the microbes were to irrupt into the surrounding tissues. In short, it is not unreasonable to think that the antisepsis vaccines might aid the surgeon in his conservative surgery, and might enable him to hold on longer when trying to save a limb.

Two further questions — questions which also cannot yet find answers—come up for consideration in this place. The one is the question whether it would not be possible in many cases to convert by physiological drainage an undrained into a drained wound, and then to obtain good results by the use of vaccines. The other is the question as to whether or no the bacteriotropic substances produced in response to antisepsis vaccines would come into operation upon sero-saprophytic microbes in corrupted discharges, and in lymph whose antitryptic power has been artificially diminished.

(5) *Employment of "Antisepsis Vaccines" in Septicæmias supervening on Wound Infections.*—On this question there is nothing that can be usefully

said other than that until scientific knowledge has progressed much beyond where it is now, it might be well to act upon the suggestion made above with regard to the possible utility of antisepsis vaccines in staving off septicæmic infections.

We now at the end of our survey come to the summary. That summary would clearly be, that the results of the inoculation of "antisepsis vaccines" have conformed in everything to scientific expectation. Of the five possible applications of vaccine therapy, the *second* and the *third* have, according to anticipation, given strikingly favourable results. The *fourth* and the *fifth*—but perhaps certain reserves may be made in connexion with the *fourth*—have given, as anticipated, very unfavourable results. And that prophylactic employment of antisepsis vaccines, which has not yet been put to probation, would seem eminently deserving of an extended and careful trial, preferably in conjunction with physiological drainage.

CHAPTER IV.

Epilogue.

And now, except for a few concluding words, I have completed what I had to say. Up to this point we have considered only the scientific problems which confront us in wound infections. What we have now to consider is how this, and similar researches, and all that new clinical experience which has been won in this war, can be made useful to the wounded.

This is a question of setting up machinery for directing and co-ordinating the work of the medical officers engaged in the treatment of the sick and wounded. And, I take it, on a question of that kind the medical profession at home will have a voice, and, if unanimous, perhaps even have a deciding voice.

In order to enable you to judge what changes in the system would be required to give effect to the idea that medical officers should bring into application the latest lessons of experience and science,

I will venture to remind you how the Medical Service of the Army is at present organised.

We have in the Army Medical Service, as it seems to me, three different and distinct services—a *Service of Administration, a Service of Hygiene and Sanitation,* and a *Service for the Treatment of the Sick and Wounded.*

The Service of Administration—and among the three services it comes easily first in order of importance—takes charge of the wounded man on the battlefield; conveys him first to the dressing station, field hospital, and clearing hospital which are ranged one behind the other at the Front; thence transports him in an ambulance train to the hospitals at the base; afterwards embarks him in a hospital ship; and, at the end of his journey, provides him with hospital accommodation at home. The Service of Administration has further to see to the feeding, clothing, bedding, nursing, and medical treatment of the man in hospital, and in transit; has to look after all manner of surgical and medical stores and equipment—besides providing in a thousand other ways for the proper working of the hospitals and hospital camps.

The *Service of Sanitation* has to protect the Army against epidemic disease by attending to water supply, conservancy, and antityphoid

inoculation. It has to keep a watchful eye on every case of infectious disease; to detect carriers; to equip, and man, the bacteriological laboratories required for this purpose; and to intervene in ways too numerous to mention to prevent the dissemination of infection.

The duties in connexion with the aforesaid services devolve almost exclusively upon the permanent officers of the Royal Army Medical Service. Their work, as every one at the seat of war knows, has been quite marvellously well done. And what stands already very high in the esteem of all the world needs no more words of praise from me.

There remains the *Service for the Treatment of the Sick and Wounded.* After supplying all the multifarious duties just enumerated, there are very few medical officers of the permanent staff of the Royal Army Medical Corps left over. Hence nearly the whole care of the sick and wounded has fallen to the civil practitioners enlisted for temporary service with the Royal Army Medical Corps. For this, if for no other reason, it must be the special concern of the civil profession to do all that in it lies to help the Medical Staff of the Army to employ to the best advantage the civil practitioners now serving as medical officers in military hospitals.

What has been done in the way of regulating the

work of these new-joined medical officers has been to transplant practically unaltered into the military hospitals the organisation under which medical practitioners work in civil life and in peace.

The treatment of the sick and wounded is committed, as it is in private and hospital practice at home, into the hands of individual practitioners, there being assigned to each a certain number of patients, or a ward. And, just as at home, where each medical man is in practically independent charge of his cases, and is free to follow whatever treatment appeals to him, so is it in the military hospitals. And just as at home the free exercise of private judgment carries with it an exclusive responsibility, saving only in those cases where a consultant is called in to advise, so also is it in the military hospitals.

Now, I submit that this unchartered freedom can work for good only in conditions such as those which surround us at home. At home, the practitioner finds himself practically always upon ground with which he is familiar. The cases which he deals with in his practice are similar to those he has seen treated in hospital. And if he should find himself upon unfamiliar ground he will, before he need take action, have time to inform himself. Moreover, though new science filters in slowly, it

does filter in. And, finally, when the medical practitioner at home makes a new experiment in treatment, he—and this is the all-important point—does learn what results. He can, therefore, profit by the teachings of experience.

Now, the conditions in military hospitals abroad are quite different from these. The practitioner is there on quite unfamiliar ground. He has to confront unfamiliar problems—problems in connexion with projectile wounds and wound infections. He has to take immediate action. He has very little opportunity to find out what has happened in similar cases. And lastly—and you will see that upon this point everything pivots—he has very little opportunity of seeing the results of his work, and learning whether his treatment has been wrong or right. For the military hospitals in France, both at the Front and also at the base, have now, through military necessity, become little more than clearing hospitals, from which cases, if at all fit to travel, are immediately sent upon their homeward journey.

There are thus lacking in the military hospitals in France all those provisos and safeguards which alone can make successful a system in which each medical man is a guide to himself. And carried out without those safeguards that system is unjust both to doctor and patient.

The doctor feels himself left in the lurch when he is not warned off from trying experiments in treatment which a hundred others have unsuccessfully tried. He fain looks for a lead where a successful treatment has been discovered. And, where there are a number of alternative treatments, he would be glad to see comparative experiments instituted to tell him which method is best. Nor is the doctor the only person interested. The patient, his relatives, and the whole nation would, once their thoughts were directed to the matter, feel that they had the vital interest in making the work of the medical officer as effective as possible.

If this is to be done it will, I believe, be necessary to make a fundamental change in the organisation of the Medical Service—to break away from the principle of free arbitrament in treatment for the Medical Officer, and to provide that all treatment shall be regulated by orders and instructions.

These are, as you see, very big issues. It is a question of a conflict between our cherished professional tradition that every medical man must be quite unfettered in his choice of treatment; and the very foundation principle of the Army, that every man shall work, not as he individually thinks best, but as part and parcel of a great machine.

The question as to which of these shall give

way to the other must, of course, be decided by the balance of public advantage. And we cannot seriously doubt as to which side that balance inclines. We have only to consider what has been achieved in this war by antityphoid inoculation, and the preventive injection of antitetanus serum; and to compare the brilliant results of these measures, enjoined as they are by direct instructions from headquarters, with the results which would have been obtained if their carrying out had been committed to the individual judgment of medical men who had not had before the war any opportunity of convincing themselves by personal experience of the utility of either antitetanus or antityphoid inoculation.

If now, as we see is the case, considerations of public utility commend the control of treatment of the sick and wounded by orders and regulations, let me in conclusion very briefly consider with you how under such a system there might be obtained a maximum of advantage with a minimum of disadvantage. I shall, of course, indicate only in very broad outlines what would seem to me to be the requirements.

I believe there would require to be a Professional Head to the Service for the Treatment of the Sick and Wounded. He would, of course, be

subordinated to the Director-General, and his duties would be to bring up the work of the medical officers everywhere to the highest standard, and to co-ordinate their work from hospital to hospital.

It would further, I think, be necessary to have an Advising Committee who should be charged with the duty of synopsising the clinical experience won in the war; of finding out what results the various therapeutic procedures had given; and of drawing up on the basis of these inquiries general instructions and recommendations for the treatment of different categories of cases. On a Committee of this sort one would, of course, wish to see representatives of surgery, of medicine, of the various specialities, and of pathology and bacteriological science. But one would wish to see the membership restricted to those who were actually at work at the seat of war, and who were prepared to take full responsibility, and carefully to watch the working of the recommendations, and at any moment to revise them in the light of accumulating experience or further laboratory experiments.

Finally, one would wish to see attached to such a committee a Research Department for the resolution of all bacteriological questions arising in connexion with hygiene, surgery, and medicine. And I may perhaps be allowed, in connexion with

this last, to point out that the Medical Research Committee of the National Insurance Act, under whom I have the honour to serve as Director of Bacteriological Researches, has, since the outbreak of the war, been placing not only large funds but a carefully selected corps of skilled workers at disposal for the prosecution of researches directly contributory to the better treatment of the wounded. It is for you to see that full advantage be taken of the results as they are obtained.

In conclusion, I desire to express my thanks to my fellow-worker, Dr. Alexander Fleming, for seeing this volume through the Press, and for contributing to it illustrations of microscopical preparations made when he was co-operating in the study of wound infections in France.

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